Micronutrients, Birth Weight, and Survival

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Key Words

pregnancy, maternal, infant, fetal growth, mortality, gestation, vitamins, minerals

Abstract

Maternal micronutrient requirements during pregnancy increase to meet the physiologic changes in gestation and fetal demands for growth and development. Maternal micronutrient deficiencies are high and coexist in many settings, likely influencing birth and newborn outcomes. The only recommendation for pregnancy currently exists for iron and folic acid use. Evidence is convincing that maternal iron supplementation will improve birth weight and perhaps gestational length. In one randomized trial, iron supplementation during pregnancy reduced child mortality in the offspring compared with the control group. Few other single micronutrients given antenatally, including vitamin A, zinc, and folic acid, have been systematically shown to confer such a benefit. A meta-analysis of 12 trials of multiple micronutrient supplementation compared with iron-folic acid reveals an overall 11% reduction in low birth weight but no effect on preterm birth and perinatal or neonatal survival. Currently, data are unconvincing for replacing supplementation of antenatal iron-folic acid with multiple micronutrients.

Contents

Low birth weight (LBW): weight less than 2500 g at birth

FGR: fetal growth restriction

Preterm birth: birth at <37 weeks of gestation

INTRODUCTION

Low birth weight (LBW; <2500 g) continues to be a major public health problem worldwide, affecting the immediate and long-term health and survival of offspring in both developed and developing countries. Although infant and under-five mortality rates have been slowly declining, the prevalence of LBW remains steady and may perhaps be increasing in some populations (60, 106). The global prevalence of LBW is estimated at ~15% but may be higher (~30% or greater) in parts of South Asia. The short-term consequences of LBW are well known and include increased perinatal and infant mortality, poor postnatal growth, and impaired immune function (65). The relationship between birth weight and infant mortality is inverse and linear, except at the higher tail of the birth weight distribution. Between the two biologic processes that underlie low birth weight—fetal growth restriction (FGR) and preterm birth—the latter may carry a higher risk of mortality (18). The majority of infants with FGR are born in developing countries, with the highest rates observed in South Asia and sub-Saharan Africa (106). Since birth weight does not capture differences in gestational age, classification of newborns according to their size-for-gestational age is often used to identify FGR. For example, small for gestational age (SGA) is defined as <tenth percentile of weight in a reference population at the same gestational age. A single cut-off of <2500 g to define LBW has been in question as maternal size (height), sex of the offspring, and other biologic factors may be important in determining the optimal size at birth (38). Birth weight, however, despite being a proxy and crude measure of newborn health, remains the most convenient measurement to take and will continue to be utilized both clinically and as a global indicator of health.

More than two decades ago, Kramer (59) showed that maternal nutritional factors may account for more than 50% of the etiology of LBW in developing countries. These factors included low prepregnancy weight, short stature, and low caloric intake during pregnancy (or weight gain) as well as maternal LBW. Not coincidentally, rates of LBW are high in settings where maternal malnutrition is common. Physiologic changes and increased metabolic demands to meet fetal requirements for growth and development make gestation a critical, nutritionally responsive period of life for both mother and fetus. On the basis of 13 randomized controlled trials, balanced energy-protein

supplementation in pregnancy has been shown to reduce FGR by 32% (20% to 43%) (61, 68) but has shown only modest, nonsignificant effects of 37.6 g (−0.21, 75.45) on mean increments in birth weight (61). These results demonstrate limited benefit of macronutrients on infant growth and have generated interest in the potential role of essential micronutrients (vitamins and minerals) for assuring adequate fetal growth and health. Given the multitude of functions of micronutrients, especially in protein and energy metabolism, it is plausible that certain individual or combinations of micronutrients may limit the effectiveness of macronutrients in enhancing birth size.

A further motivation for enhancing birth size stems from research advances in the area of developmental origins of health and disease, which have now well demonstrated that lower or suboptimal birth weight may contribute to coronary heart disease, stroke, hypertension, and type 2 diabetes through fetal programming that makes individuals more susceptible to environments of excess later in life (5). Fetal development is a period of plasticity, which allows for the phenotype to respond to environmental cues such as energy (and potentially micronutrient) restriction (40, 112). Therefore, improving birth weight through micronutrient interventions may confer both short- and long-term benefits for the offspring.

This review examines the evidence for the contribution of micronutrient deficiencies in fetal growth, gestational length, and infant mortality, focusing on the literature among non-HIV-1 populations.

MATERNAL MICRONUTRIENT DEFICIENCIES IN PREGNANCY: BURDEN AND CAUSES

Multiple, not single, micronutrient deficiencies are likely to affect women of reproductive age, especially during pregnancy. Micronutrient deficiencies in pregnant women continue to be a major public health problem in low-income countries for a variety of reasons. These include poor access to a nutrient-adequate diet due to low income, bioavailability, and seasonality; increases in metabolic and physiologic demands of pregnancy; cultural practices; and infections. Micronutrients are essential for growth, metabolism, and cell differentiation, but only a few specific nutrients have received appreciable study in human pregnancy (12, 32). The global prevalence of maternal vitamin A deficiency is estimated to be 18.4% using serum or breast milk vitamin A concentrations of <1.05 μmol/L; it is estimated to be 5.8% using the indicator of night blindness during pregnancy (111). The global prevalence of anemia among pregnant women is estimated at 42% (27), with approximately half of the anemia attributable to iron deficiency.

Multiple, concurrent deficiencies when examined in a few populations are seen in high proportions (50, 80). For example, in Nepal, multiple deficiencies coexisted in early gestation, when the impact of hemodilution on serum concentrations was minimal (**Figure 1**). Prevalence rates of low serum concentrations were high for zinc, iron, and B-complex and other vitamins, with more than 80% of women experiencing at least two micronutrient deficiencies (50). Similarly, a survey from a rural area of Haryana State of India found deficiencies to be concurrent in late pregnancy, especially those of iron and zinc (80). Dietary intake data collected as part of this study also found that 75%–100% of women were consuming less than the recommended daily allowance (RDA) for folic acid, zinc, iron, copper, and magnesium. In rural Shaanxi, China, semiquantitative food frequency questionnaire data revealed inadequate intakes of folate (97%), zinc (91%), and iron (64%) in pregnant women (17). In peri-urban Mexico, prevalence of zinc and folate deficiency in the third trimester was 34% and 19%, respectively, and that of low vitamin A status was 17.6% among women in the control group of a micronutrient trial (37). Despite some data available to demonstrate widespread micronutrient deficiency in pregnancy, few representative studies have examined the status of a wider range of micronutrients.

Small for gestational age (SGA): birth weight less than the tenth percentile of weight for a given gestational age in a reference population

MECHANISMS AND PATHWAYS BY WHICH MICRONUTRIENTS MAY INFLUENCE FETAL GROWTH AND GESTATIONAL DURATION

Fetal growth is a complex process influenced throughout gestation by the maternal environment, both nutritional and health, and genetic endowment and the interaction between the two. These pathways and the influence of micronutrients are not well understood in humans. Although peak gains in fetal length occur during the second trimester, gains in weight are greatest in the third trimester, as fat and muscle and pools of nutrient stores are deposited to a large extent in the final stages of pregnancy (109). Birth weight is the summary measure of the interactions between these factors in a live born infant, and a given size at birth may result from a wide variation in intrauterine growth trajectory and body dimension and composition; at a given birth weight, organ size, development, and maturity may vary (45). Among the many aspects of the dynamic materno-placento-fetal environment, several are believed to exert a particular influence on birth and postnatal outcomes, including the efficiency and adequacy of maternal plasma volume expansion, placental endocrine factors, hormonal balance and metabolism within the fetus, and materno-fetal nutrient transfer. Gene imprinting and epigenetic mechanisms also play a role in early embryonic life and perhaps even prior to and during implantation. To what extent micronutrients may influence fetal growth and gestational age through these pathways is elucidated below, with the caveat that limited data are available from human studies (**Figure 2**).

Epigenetic Factors and Gene Imprinting

In humans and other mammals, imprinted genes—a class of genes found in the placenta and fetal tissues—appear to have a critical role in feto-placental development. Genomic imprinting is the expression of a single allele of a gene of maternal or paternal origin. Reik et al. (89) proposed that imprinted genes in the placenta control the supply of nutrients, whereas

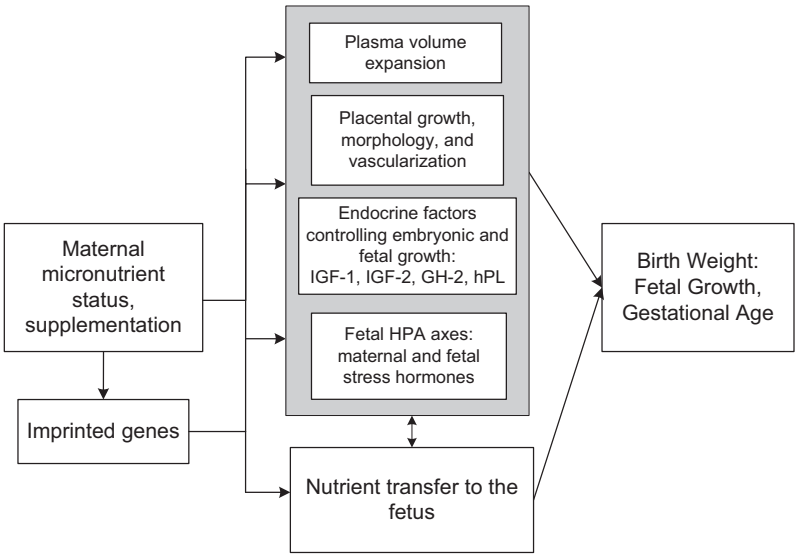

Figure 2

Conceptual framework for the pathways linking maternal micronutrient status and birth weight. GH-2, growth hormone 2; hPL, human placental lactogen; IGF, insulin-like growth factor.

in the fetal compartment they control nutrient demand by regulating fetal growth. The action of imprinted genes in regulating nutrient transfer involves the growth and transport capacity of the placenta and the modulation of nutrient requirements by the fetus, mainly through the control of fetal growth (89). Imprinting is controlled epigenetically by differential DNA methylation, which in turn can be influenced by environmental factors including nutrition. In particular the reciprocally imprinted Igf2-H19 gene complex (H19 is the silent paternal allele) may play a central role in matching the placental nutrient supply to the fetal nutrient demands for growth (34). Gene imprinting is also one of the early factors affecting placental growth, vasculature, and transport capacity (34). Availability of methyl donors such as vitamin B12, folic acid, and some amino acids during pregnancy has been found to alter DNA methylation in experiments in mice (110, 112), although the implications of these mechanistic experiments to humans are not well understood.

Plasma Volume Expansion

One of the earliest adaptations that occurs in pregnancy involves the expansion of blood volume and related hemodynamic changes that are the key to facilitating growth. The expansion of maternal plasma volume increases uterine and placental blood flow, which in turn allows for adequate transport of nutrients and oxygen to the fetus (29). Plasma volume increases progressively by about 1250 mL from 6 weeks until about 34 weeks gestation (10, 49). Red cell mass also increases, but to a lesser extent, and it lags behind, resulting in the physiologic anemia of pregnancy. Inadequate plasma volume expansion is associated with preeclampsia and fetal growth restriction (96, 97, 108), and women who are underweight have a higher risk of poor plasma volume expansion and resulting poor fetal growth (95). In general, however, our understanding of other factors influencing this physiologic change is inadequate. One clinical implication of this change is that high nutrient concentration during pregnancy may reflect either adequate nutritional status or poor expansion.

Placental Factors

Placental growth, vascularization, and function is also key for nutrient transfer and, ultimately, optimal fetal growth and weight at birth (88, 94). The capacity to exchange nutrients is partially dependent on vascularization of the placenta, which in turn affects uterine and umbilical blood flow (88). Women with growth-restricted fetus exhibit smaller placentas and reduced uterine blood flow (76). In terms of weight, the majority of placental growth is completed by the end of the second trimester (88), and placental volume is then strongly correlated with fetal weight (13, 56, 103). Maternal prepregnancy weight and weight gain early in pregnancy also influence placental volume (56, 102).

There is some evidence that maternal micronutrient intake will improve placental growth. In a study in Pune, India, higher placental weight in women was associated with eating more micronutrient-rich foods (green leafy vegetables, fruits, or milk products) (87), whereas in a large, randomized trial of multiple micronutrient supplementation, significant but small (9 g, 95% CI: 4–14 g) increases in placental weight at birth were observed among the intervention versus control subjects, albeit women were at ~21 weeks gestation when supplementation commenced (33).

Angiogenesis, the formation of new blood vessels from existing ones, is a process essential for the vascularization of the placenta (1, 91). Proper angiogenesis is associated with uterine and umbilical blood flow and therefore placental growth and transfer nutrients (90). Several factors and their receptors have been identified in angiogenesis, including vascular endothelial growth factor (VEGF), placental growth factor (PlGF), basic fibroblast growth factor-2 (FGF-2), soluble VEGFR-1, and angiopoietin (1), but it is unclear whether micronutrients can influence their expression or function. Placental

synthesis of nitric oxide—a major vasodilator and angiogenesis factor—may be impaired with maternal undernutrition in pigs, thus leading to inadequate fetal growth (113), but such evidence is needed in humans.

Endocrine Factors

There is a strong connection between the endocrine axes and fetal somatotrophic growth (39, 73). The dominant fetal growth regulator in later gestation is insulin-like growth factor 1 (IGF-1), produced by the fetal liver and tissues in response to glucose concentrations (75), and changes in IGF-1 may also reflect protein metabolism (104). The fetal IGF-1 system is sensitive to maternal nutritional status as shown in animal studies (41). For example, in sheep, short-term maternal undernutrition leads to reduced IGF-1 and altered IGF-1 binding proteins (6). There are no published studies linking maternal micronutrient status with these endocrine factors controlling fetal growth in humans.

Placental growth hormone or GH2 also plays several roles, including trophoblast invasion, but its key role is somatotrophic (36). Additionally, GH-2 directly affects placental development and function, and its concentrations are decreased in mothers of infants with FGR (70). GH-2 is highly correlated with IGF-1, which is the proposed mechanism for its influence on growth (16, 66) and also stimulates maternal anabolism, presumably to mobilize nutrients for transfer to the fetus (4). Although a direct association to micronutrient status has not been identified, there is a link between glucose concentrations and secretion of GH-2 (4). Human placental lactogen (hPL) along with GH-2 are believed to create peripheral insulin resistance in the mother that allows preferential glucose supply to the fetus (41). In sheep, periconceptional, but not later, undernutrition results in altered hPL production and premature activation of the hypothalamic pituitary adrenal (HPA) axis, resulting in premature delivery (see below).

Fetal Hypothalamic Pituitary Adrenal Axis

Fetal exposure to exogenous glucocorticoids is known to impair fetal growth in animals (9), and increased levels have been observed in response to maternal protein malnutrition and poor placental function and blood flow (42, 67). The placental enzyme 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) is a crucial barrier, protecting the fetus from high maternal concentrations of cortisol by inactivating it to cortisone (9). Maternal levels of cortisol are 5–10 times higher than levels in the fetus, and when the placenta is functioning normally, the majority of maternal cortisol is converted to cortisone before crossing (72). Late in gestation, the fetal adrenal gland secretes cortisol, and near term, 75% of circulating cortisol is of fetal origin, whereas cortisone is mostly from the mother (8). Retinoic acid has been shown to stimulate production of 11β-HSD2 through mRNA expression (105). Maternal anemia (causing hypoxia) and iron deficiency may induce stress as well as elevated corticotropin-releasing hormone, which is known to increase the risk of preterm labor in animals (3). Corticotropin-releasing hormone also has a role in placental vasodilation through regulation of nitric oxide, a relationship impaired in preeclampsia (52). Few other micronutrient deficiencies have been examined for their role in inducing fetal stress.

Maternal Nutrient Status and Transfer

Many micronutrient requirements increase during pregnancy to meet the nutrient supply to the fetus. A complex relationship exists between maternal nutrient intake (i.e., diet) and fetal nutrient uptake (32). Partitioning of nutrients in pregnancy is controlled by homeorhetic mechanisms (7) such that if nutrients are limited, the placenta and fetus receive priority over most other maternal tissues when nutritional status is adequate or mildly lacking (88). This strategy is reversed when maternal deficiency is

severe, in which case the health and survival of the maternal organism is preserved (57).

There is much lacking in our understanding of nutrient transfer to the fetus. Micronutrients are often transferred to the fetus against the concentration gradient (e.g., iron and zinc), but not always (e.g., vitamins A and E). Correlations between maternal and cord blood levels have been observed for some nutrients, including vitamin E, B_{12}, and folate (55, 62), but to what extent this impacts fetal size is not well understood. A trial of zinc supplementation in Peru found higher zinc concentrations in maternal and cord serum from treatment but no improvement in birth weight (14). Lower levels of folate, riboflavin, vitamin A, and vitamin E in the cord blood have been associated with FGR/SGA (62, 74), but causality cannot be attributed. For instance, in FGR, the normal relationship between maternal and fetal levels may be altered (presumably from poor placental function) (62). In one study among Pakistani women, much lower concentrations of folate were found in the cord blood of FGR versus normal-weight infants, and fetal folate correlated with maternal levels ($r = 0.63$, $p < 0.01$) in normal-weight infants but not in FGR infants ($r = 0.0$), implying placental dysfunction and abnormal nutrient transfer (62).

Observational studies conducted in Indian and Danish women have shown that women who eat more micronutrient-rich fruits and vegetables during pregnancy deliver infants with higher birth weights (69, 87), but causal inference is lacking.

SUMMARY OF THE IMPACT OF SINGLE MICRONUTRIENTS ON BIRTH WEIGHT AND INFANT MORTALITY

Few vitamins and minerals when provided singly during the fetal period via maternal supplementation seem to show consistent benefits on birth outcomes, including birth weight and infant survival (28, 32, 68, 85). An exception to this may be iron, for which the strongest evidence for a beneficial effect has now been accumulated via findings of several randomized controlled trials. Two of these were well-designed trials done in the United States among nonanemic, iron-sufficient women at enrollment. In these trials, supplementation during pregnancy with iron compared to a placebo significantly increased birth weight (by 100 to 200 g) (27, 100). Further, iron supplementation reduced the incidence of low birth weight in both studies, gestational age in one study (27), and preterm in the other (100). In a cluster-randomized controlled trial in Nepal, antenatal iron-folic acid supplementation (but not folic acid alone) significantly reduced the incidence of low birth weight by 16% (21), although the small reduction of ~20% in three-month infant mortality was not significant (26). Recently, in a follow-up study in this trial, child mortality from birth to 7 years of age was found to be significantly reduced by 31% (hazards ratio: 0.69, 95% CI: 0.49, 0.99) in the offspring of mothers who had received iron-folic acid during pregnancy relative to the controls (25), revealing for the first time the benefit to child survival of antenatal iron supplementation in an iron-deficient setting.

In a trial in China, maternal supplementation with iron-folic acid compared with folic acid alone used as the control significantly reduced early preterm (<34 wk) delivery (relative risk = 0.50, 95% CI: 0.27, 0.94) and neonatal mortality (RR = 0.53, 95% CI: 0.29, 0.97), although the impact on birth weight was not significant (115).

A recent Cochrane meta-analysis of antenatal iron-folic acid supplementation found a 36 g (−5, 77 g) increase in mean birth weight, a 21% reduction in LBW (RR = 0.79, 95% CI: 0.61, 1.03), and a 15% reduction in preterm birth (RR = 0.85, 95% CI: 0.67, 1.09) (81). Although all three treatment effects were nonsignificant, the point estimates are suggestive of a beneficial impact. One concern with the analysis is that it includes several extremely small studies of sample sizes <20 per group that showed 100–300 g lower weight in the iron-folic acid group compared with the control and does not include the recent study from China (115).

Since antenatal iron supplementation is already a policy in many countries, it is relevant to show that iron use is beneficial for enhancing birth outcomes in a programmatic context. This was recently demonstrated in Zimbabwe with data from the national Demographic and Health Survey (DHS). Iron use during pregnancy in this study was found to be associated with a mean 103 g (42, 164 g) increase in birth weight adjusted for confounding variables (71).

Findings with regard to the contribution of other micronutrient deficiencies to birth outcomes are limited, and evidence for any beneficial effects is patchy. Folic acid is often included in iron supplements for antenatal use, but on its own does not seem to confer a benefit for birth weight or gestational duration (21, 68). Thus, when iron and folic acid are combined, any benefit to hematologic status, birth weight, and preterm can safely be attributed to iron alone. Antenatal vitamin A supplementation has also been found to show no impact on either birth weight or infant mortality (30, 54).

Zinc supplementation trials have found little benefit of maternal supplementation during pregnancy on birth outcomes or maternal health (77). A recent Cochrane meta-analysis combining 13 randomized controlled trials showed a small but significant reduction in preterm delivery associated with zinc supplementation (RR = 0.86, 95% CI: 0.76, 0.98), although no similar reduction was observed in the rates of LBW or other neonatal or maternal outcomes (63). The authors concluded that the reduction in preterm delivery could be reflective of poor nutrition in general and that zinc supplementation during pregnancy would not be recommended based on these results. This may be prudent, as in some studies adding zinc to the currently recommended antenatal iron-folic acid supplement has attenuated the efficacy of iron on birth weight and infant mortality outcomes (21, 26). On the other hand, in a recent review of zinc supplementation during pregnancy, the addition of zinc to iron-folic acid is recommended for consideration, but more definitive research is called for to demonstrate an additive benefit (47).

A promising trace element for enhancing birth weight may be magnesium, but it has received little attention as an intervention for pregnancy. A meta-analysis of magnesium trials suggests a reduction in low birth weight and SGA of about 30%; however, all but one trial included in the meta-analysis were from developed countries (68). Only observational studies are available to examine the role of maternal vitamin D status, which is not consistently associated with birth weight (32, 58, 82). Maternal adaptations during pregnancy may partly be an explanation, as total 1,25(OH)D concentrations double or triple in maternal circulation beginning in gestation, which can influence calcium absorption (58). Limited data from trials exist for the role of other vitamins, including vitamins E and C, and B-complex vitamins, which are required cofactors for energy metabolism (32, 85).

In summary, beyond iron, the evidence for other micronutrients for enhancing birth weight and gestational length, although biologically plausible and supported by observational studies and animal experimentation, is weak. For some nutrients, such as folate, vitamin A, and perhaps zinc, trial data are adequate and reveal no evidence for a benefit, whereas for others, such as magnesium and vitamin D, more research may be needed. For many micronutrients, such as B-complex vitamins, vitamins D, C, E, and others, there is a lack of sufficient data demonstrating the burden of deficiencies, especially in developing countries, where these micronutrients are likely to be limiting and may influence birth outcomes. However, it is probably unlikely that large, rigorous trials of single nutrients will be undertaken considering the momentum toward multiple-micronutrient intervention strategies for pregnant women in developing countries (see below).

SUMMARY OF THE IMPACT OF MULTIPLE-MICRONUTRIENT SUPPLEMENTATION TRIALS ON BIRTH WEIGHT AND INFANT MORTALITY

In developed countries, women routinely use a one-a-day prenatal multivitamin and mineral supplement during pregnancy. However, few controlled clinical trials are available from developed countries demonstrating the beneficial impact, if any, of such supplement use on outcomes such as birth weight, length of gestation, and infant and maternal morbidity and mortality. An older systematic review of 17 trials of iron and vitamins exists, showing that beyond some modest benefits of reduced preeclampsia and fewer deliveries before the fortieth week in one to two studies, none of the studies reported any benefit for other outcomes (46). Notably, most studies were identified to have methodological and reporting errors and suffered from low sample sizes. The practice of prenatal vitamin and mineral supplement use, which is ubiquitous in high-income countries, remains rare among the poor of the developing world, where the burden of micronutrient deficiencies and poor birth outcomes is high and antenatal care is poor. It stands to reason that mothers and infants in this region may respond favorably to reductions in materno-fetal micronutrient deficiencies through antenatal supplementation. And yet, the full health benefits and safety of supplying prenatal multiple micronutrients, especially across different high-risk populations, are not fully elucidated.

In recognition of this and of the need to test the efficacy of a single formulation of a multiple-micronutrient supplement for use during pregnancy in developing countries, United Nations Children's Fund (UNICEF), United Nations University, and the World Health Organization (WHO) convened a technical meeting in 1998 to discuss and propose a formulation of such a prenatal micronutrient supplement. Thus, the supplement (called UNIMMAP, for United Nations International Multiple Micronutrient Preparation) was created, containing 15 micronutrients at dosages that approximated the RDAs for pregnancy (107). Over the past decade or so, 12 randomized controlled trials of multiple-micronutrient supplementation (MMS) have been undertaken to examine, in most cases, the additional benefit of MMS over iron-folic acid alone (usually standard of care or policy) in improving birth weight and other birth outcomes. Many of these studies were coordinated by UNICEF, although some investigators tested formulations slightly different from the UNIMMAP. These trials were conducted in developing countries—in South Asia, Africa, and Latin America—among largely non-HIV women who were supplemented daily from early to mid pregnancy through three months postpartum in most studies. Although perinatal and neonatal mortality were assessed in several trials, few studies were powered to examine treatment effects on mortality as an outcome. This section summarizes the findings of these trials and the results of three meta-analyses that have been conducted using data from these trials.

MMS: multiple-micronutrient supplementation

Table 1 summarizes the study design, populations, and main results from the published trials. In one of the first trials in Mexico, where women were randomized to receive either iron (60 mg) or MMS containing the same amount of iron plus 11 other nutrients, there was no difference in the mean birth weight and gestational age between the two groups (83). MMS was associated with increased weight retention during the postpartum period among overweight women, whereas the nonoverweight women lost weight (84). A study in Zimbabwe that included both HIV-1-infected and uninfected pregnant women found a small increase in birth weight due to MMS versus placebo (49 g; −6, 104 g), but it found no reduction in LBW (35). The treatment effect differed by maternal HIV status; 26 g (−38, 9 g) in HIV-negative women compared with 101 g (−3, 205 g) among HIV-positive women (35). In this study, all women received 60 mg of iron and 400 μg of folic acid separately as per the national policy. A trial in

Table 1 Maternal multiple micronutrient supplementation effects on birth weight, low birth weight, preterm delivery, and neonatal mortality

Study	Population	Study design/groups	Birth weight Mean (SD), diff (95% CL), g	LBW% RR (95% CL)	Preterm birth,% RR (95% CL)	Neonatal mortality per 1000 births, RR (95% CL)	Comments
Ramakrishnan et al. 2003 (83)	Mexico, semiurban	Control: Fe (n = 323) MM (n = 322) MM versus control	2977 (393) 2981 (391) -	8.89 8.49 -	6.54 7.48 -	Not reported	Acceptable nutritional status. Low LBW rates
Christian et al. 2003 (21, 26)	Nepal, Sarlahi, rural	Control: VA (n = 685) FAFe: (n = 635) MM (n = 705) FAFe versus control MM versus control	2587 (445) 2652 (436) 2659 (446) 37 (−16, 90)[a] 64 (12, 119)[a]	43.4 34.3 35.3 0.84 (0.72, 0.99) 0.86 (0.74, 0.99)	20.4 23.1 20.6 1.13 (0.90, 1.40) 1.01 (0.82, 1.26)	45.7 36.3 54.0 0.80 (0.50, 1.27) 1.19 (0.77, 1.83)	Number for mortality outcome is: 876, 772, & 870 for control, FAFe & MM
Friis et al. 2004 (35)	Harare, Zimbabwe antenatal clinics: HIV-negative	Control: PL (n = 361) MM (n = 364) MM versus PL	3044 3070 26 (−38, 91)	9.7 7.1 0.74 (0.45, 1.20)	16.2 12.7 0.79 (0.55, 1.13)	Not reported	Women received iron-folic acid; high loss to follow-up
Kaestel et al. 2005 (51)	Guinea-Bissau, antenatal clinics	Control: FeFA (n = 366) MMx1RDA (n = 360) MM2xRDA (n = 374) MM1 versus FeFA MM2 versus FeFA	3022 3055 3097 49 (−22, 121)[b] 88 (17, 159)[b]	13.6 12.0 10.1 0.88 (0.57, 1.37)[b] 0.70 (0.44, 1.11)[b]	Not reported	42 50 44 1.15 (0.63, 2.10)[b] 1.09 (0.60, 1.99)[b]	Birth weight missing for 974 infants
Osrin et al. 2005 (79)	Nepal, Dhanusa, urban/ rural, antenatal clinics	Control: FeFA (n = 523) MM (n = 529) MM versus control	2733 (422) 2810 (529) 77 (24, 130)	25 19 0.69 (0.52, 0.93)	10 8 0.85 (0.57, 1.29)	20 30.6 1.53 (0.72, 3.23)	Number for mortality outcome: 568 and 571 for control and MM
Zagre et al. 2007 (114)	Niger, rural	Control: FeFA (n = 1222) MM (n = 1328) MM versus control	3025 (205) 3092 (190) 67 (51, 82)	8.4 7.2 −1.2 (−1.8, −0.6)[e]	Not assessed/ reported	Not assessed/ reported	

Shankar et al. 2008 (99)	Indonesia, Lombok	Control: FeFA (n = 15,486) MM (n = 15,804) MM versus control	3176 3198 21 (−11, 53)	11 9 0.86 (0.73, 1.01)	Not assessed/ reported	25.5 22.3 0.90 (0.76, 1.06)	Birth weight measured in a subgroup of 11,101; 3-month mortality significantly reduced by 18%
Zeng et al. 2008 (115)	China, rural	Control: FA (n = 1545) FeFA (n = 1470) MM (n = 1406) FeFA versus control MM versus control	3154 (445) 3174 (424) 3197 (438) 24 (−10, 59)[c] 42 (7, 77)[c]	5.3 4.5 4.1 0.81 (0.59, 1.12)[c] 0.78 (0.56, 1.08)[c]	6.1 4.9 5.2 0.79 (0.58, 1.07) 0.86 (0.64, 1.14)	20.2 10.7 12.3 0.53 (0.29, 0.97) 0.61 (0.34, 1.10)	Impact of FAFe significant for early preterm
Roberfroid et al. 2008 (92)	Burkina Faso, rural	Control: FeFA (n = 628) MM (n = 632) MM versus control	2877 (424) 2914 (450) 41 (−11, 94)	15.6 14.6 0.91 (0.65, 1.28)[d]	13.4 14.2 1.04 (0.75, 1.45)[d]	10 19 2.1 (0.78, 5.67)[d]	Difference in perinatal mortality was marginally significant
Sunawang et al. 2009 (101)	West Java, Indonesia	Control: FeFA (n = 341) MM (n = 384) MM versus control	3054 (419) 3094 (438) 40 (−22, 103)	6.3 7.3 0.84 (0.47, 1.50)	Not assessed	42 23 0.54 (0.20, 1.20)	
Bhutta et al. 2009 (11)	Karachi, Pakistan, periurban	Control: FeFA (n = 1230) MM (n = 1148) MM versus control	2880 (500) 2950 (600) 70	19.6 17.7 NS	Not reported	23.5 43.2 1.64 (0.94, 2.87)	Difference in early neonatal mortality was significant

Low birth weight: <2500 g.

Preterm delivery: gestational duration of <37 wk.

[a]Adjusted for maternal weight at baseline.

[b]Adjusted for malaria parasitemia, anemia, infant sex, and seasons of birth.

[c]Adjusted for multiple births and cluster randomization.

[d]Adjusted for malaria prevention and health center.

[e]Absolute difference.

CL, confidence limits; FA, folic acid; Fe, iron; MM, multiple micronutrient; PL, placebo; RR, relative risk; SD, standard deviation; VA, vitamin A.

Guinea-Bissau that used one and two times the RDA of nutrients in the multiple micronutrient supplements compared with iron-folic acid as control showed no impact on birth weight with the single-RDA formulation (53 g, −19, 125); however, supplementation with the formulation that provided twice the RDA for each nutrient increased birth weight by 95 g (25, 167 g), although adjustment attenuated this effect (51). No difference in perinatal or neonatal mortality was observed with the increased birth weight, although the study was not large enough to show differences in this outcome, and the loss to follow-up was high (51).

One of two double-blind trials in Nepal was conducted in the southern plains District of Sarlahi and compared four combinations of micronutrients taken from early pregnancy through three months postpartum to a control supplement (21, 26). The test supplements contained folic acid alone, folic acid+iron, folic acid+iron+zinc, or a multiple-micronutrient formulation with folic acid+iron+zinc and 11 other micronutrients. All supplements also contained vitamin A, with vitamin A alone being the control. Folic acid supplementation did not increase birth weight. The combination of iron-folic acid increased mean birth weight and reduced LBW (RR = 0.84, 95% CI: 0.72, 0.99), but adding zinc antagonized beneficial effects of iron, and the impact on low birth weight was attenuated (RR = 0.96). MMS resulted in the greatest increase in mean birth weight of 64 g (95% CI: 12, 115 g). The three-month infant mortality rate in this trial was 55.9% in the control group and, although nonsignificant, was lower by about 20% in the folic acid and folic acid+iron groups but not in the multiple-micronutrient supplement group (59.8%) (26). Among preterm infants, mortality was lowered significantly (by over 40%–60%) with the folic acid and iron-folic acid supplement combinations ($p < 0.001$).

A second randomized trial, conducted also in Nepal in the District of Dhanusa but based out of a clinic, compared the UNIMMAP formulation with iron-folic acid and reported a significant increase in birth weight (77 g, 95% CI: 24–130) due to MMS (79). However, the increase in birth size did not result in improved infant survival. Data from the two Nepal trials were pooled to estimate the impact of MMS compared to iron-folic acid on fetal loss and infant mortality that neither study was independently powered to examine (22). The pooled analysis of the two Nepal studies showed significant increases of 36% and 52% in perinatal and neonatal mortality, respectively, associated with MMS compared with iron-folic acid.

Other trials of MMS in South Asia were conducted in Bangladesh and Pakistan (11). Although the Bangladesh data remain unpublished, both these studies using the UNIMMAP formulation have failed to find an impact of MMS on low birth weight, and the study in Pakistan even showed that the neonatal mortality rate was somewhat higher in the MMS group compared with the iron-folic acid group (RR = 1.64, 95% CI: 0.94, 2.87) (11).

In a trial in Niger, the UNIMAPP supplement increased mean birth weight by 67 g (51, 82 g) versus iron-folic acid, although 30% of the data were missing (114). In Burkina Faso, the UNIMMAP supplement increased both birth weight (52 g, 4, 100 g) and length (3.6 mm, 0.8, 6.3 mm), but only after adjustment of gestational age at delivery (92). The risk of perinatal mortality was marginally significantly increased in this study with the MMS (OR = 1.78, 95% CI: 0.95, 3.32, $p = 0.07$) and more so in primiparous women (OR = 3.44, 95% CI: 1.1, 10.7), an increase previously observed in the two studies in Nepal and Pakistan.

In Indonesia, a large trial (called SUMMIT) involving 31,290 pregnant women had findings that differed from the other trials of MMS (99). In this trial, there was no impact of MMS on birth weight (21 g, −11, 53 g), LBW rate (11% in the MMS versus 9% in the iron-folic acid group, $p > 0.05$), or perinatal or neonatal mortality, but early infant mortality (through 3 months of age) was reduced by 18% (RR = 0.82, 95% CI: 0.70, 0.95). In a second trial, in West Java, Indonesia, the UNIMMAP supplement did not have a significant impact on birth

weight (3094 g in the MMS versus 3054 g in the iron-folic acid control, $p > 0.05$) or neonatal mortality (101).

Finally, in a trial in China of 5828 pregnant women and 4697 live births, women were randomized to daily folic acid (control) versus iron-folic acid or MMS. Iron-folic acid supplementation was not associated with an increase in birth weight (24 g, −10, 59 g) whereas MMS increased birth weight by 42 g (7, 78 g) (115). On the other hand, iron-folic acid increased the length of gestation (by 0.23 wk, 0.10, 0.36), as did MMS (0.19 wk, 0.06, 0.32 wk). Furthermore, iron-folic acid, unlike MMS, reduced early neonatal mortality by 54% (RR = 0.46, 95% CI: 0.21, 0.98), although these analyses were posthoc (115).

Two other studies that used either a more unconventional supplement formulation or a more selected population group are also worth noting. One was a double-blind randomized trial among HIV-negative women in Tanzania (33). In this study, women received a daily multivitamin supplement (containing multiples of RDA of vitamins) or a placebo during pregnancy. The difference in birth weight between supplement groups was 67 g ($p < 0.001$), and there was a reduction in LBW by 18% (RR = 0.82, 95% CI: 0.70, 0.95). There was no impact on preterm birth, but SGA births were significantly reduced. In another small study done in a clinic in Delhi, India, 200 pregnant women with body mass index (BMI) <18.5 kg/m^2 or with hemoglobin 7–9 g/dL were enrolled in late gestation to receive a supplement containing 29 vitamins and minerals or a placebo (98). A strong treatment effect was observed with an increment of 98 g (−16, 213 g) in birth weight, which was not significant due to the small sample size. However, the incidence of LBW declined by 70% (RR = 0.30, 95% CI: 0.13, 0.71) and that of early neonatal morbidity by 58% (RR = 0.42, 95% CI: 0.19, 0.94). The results from these studies may not be generalizable because they both used unconventional supplement formulations, and one of the studies was done in a small select group of high-risk women.

Three meta-analyses have now been conducted of these trials, although only the most recent one includes all of the 12 trials done in developing countries discussed above (64). The first one was a systematic Cochrane analysis undertaken by Haider & Bhutta (44) of published (n = 6) and at that time unpublished (n = 3) trials of MMS. This analysis compared two or more nutrients with a placebo, no supplement, or a supplement with a single nutrient. A subanalysis also compared multiple micronutrients with iron-folic acid. The main conclusion of this review was that the evidence to suggest that iron-folic acid should be replaced with multiple micronutrients was lacking and that further research was needed to demonstrate either benefit or potential adverse effects of a multiple micronutrient supplement. The second meta-analysis included data from developed countries and HIV-1 infected populations and found prenatal MMS to increase birth weight and reduce LBW compared with placebo or iron-folic acid as control (43). There was no evidence of a significant impact on SGA or preterm birth, and mortality was not examined as an outcome.

In October 2005, UNICEF, WHO, and the UN Standing Committee on Nutrition commissioned a systematic review team to undertake a meta-analysis of 12 trials conducted in developing countries to examine the impact of antenatal MMS compared with iron-folic acid on birth outcomes and neonatal survival (31, 64, 93). The pooled estimates for birth weight and fetal growth outcomes were as follows (**Table 2**): MMS increased mean birth weight (22.4 g, 95% CI: 8.3 to 36.4; p = 0.002), reduced LBW (OR = 0.89, 95% CI 0.81–0.97; p = 0.01) and SGA birth (OR = 0.90, 95% CI 0.82–0.99; p = 0.03), and increased large-for-gestational-age birth (OR = 1.13, 95% CI 1.00–1.28; p = 0.04) (31). There was no significant impact on birth length, duration of gestation, or the risk of preterm. There was also no reduction in stillbirth, perinatal mortality, or neonatal mortality. There was a suggested higher risk of early mortality with MMS compared with iron-folic acid, although not statistically significant (OR 1.23,

Table 2 Results of a meta-analysis of the effects of antenatal multiple micronutrient supplementation versus iron-folic acid on birth outcomes in 12 randomized controlled trials in developing countries (31, 93)

Birth outcome	Pooled effect size (95% CI)
Birth weight, g	22.4 (8.3, 36.4)
Low birth weight (<2500 g)	0.89 (0.81, 0.97)
Small for gestational age	0.90 (0.82, 0.99)
Large for gestational age	1.13 (1.00, 1.28)
Gestational age, days	0.17 (−0.35, 0.70)
Preterm delivery (<37 weeks)	1.00 (0.93, 1.09)
Stillbirths	1.01 (0.88, 1.16)
Perinatal mortality	1.11 (0.93, 1.33)
Early neonatal mortality	1.23 (0.96, 1.59)
Late neonatal mortality	0.94 (0.73, 1.23)

95% CI 0.96–1.59) (93). Maternal prepregnancy BMI modified the treatment effect; MMS increased birth weight only among women with higher BMI (>20 kg/m^2). Exclusion of the large Indonesian study (99), which also found no significant impact of MMS on perinatal or neonatal mortality, resulted in a significant increase in early neonatal mortality in the pooled analysis. Thus, the meta-analysis of the 12 MMS trials found a small, modest increase in birth weight, an 11% reduction in low birth weight, but no impact on neonatal survival. This suggests that current evidence for replacing antenatal iron-folic acid with a multiple micronutrient supplement is weak.

INTERPRETATION OF RESULTS, PLAUSIBLE MECHANISMS, AND NUTRIENT INTERACTIONS

The findings from the trials described above show equivocal benefits of antenatal multiple-micronutrient supplements, and perhaps it would be appropriate to raise safety concerns regarding their use for women in the developing world. That such an intervention was systematically and extensively examined across various population groups in developing country settings is commendable and provides the much-needed data on the efficacy and safety of a one-a-day micronutrient supplement for pregnant women.

First, it may be useful to examine the appropriateness of the amount and mix of nutrients in the formulation—the UNIMMAP—that was tested in a majority of the studies. Many of these studies tested a multiple micronutrient supplement compared with the currently recommended iron-folic acid supplement as control. As described previously, beyond iron, there is limited evidence that other micronutrients are important for enhancing birth outcomes. Thus, the scientific rationale for each essential micronutrient added in the mix is the theoretical increased need for these nutrients during pregnancy and the need for correcting underlying deficiencies. In settings where some micronutrients (such as iron) are more limiting for fetal growth and other outcomes, it is important to consider whether nutrient-nutrient synergies or antagonisms are likely to play a role. Related to this, the negative interaction between iron and zinc may be relevant to examine, especially in settings where iron deficiency during pregnancy is common and limiting. The studies in Nepal and China, for example, in which iron-folic acid was independently assessed, found this combination to yield better outcomes with regard to birth weight than did the combination with added zinc (21) or with regard to survival compared to added multiple micronutrients that included zinc (21, 115). In two studies that evaluated maternal iron and hematologic indicators as outcomes, MMS did less well compared with iron (alone or with folic acid) (24, 86).

The UNIMMAP supplement contains 30 mg of iron, which, although close to the U.S. Institute of Medicine RDA for iron in pregnant women (27 mg), is half the amount recommended for antenatal supplementation in developing countries (107). The rationale for the lower dosage was that other vitamins in the supplement would likely enhance iron metabolism (107). However, data from the above two studies provided no evidence in support of this. It may be argued that the amount of iron in the MMS was too low in some settings, such as

Pakistan, where the rates of severe anemia during pregnancy are high (10%) despite the absence of malaria (23). On the other hand, the study in Bangladesh, which compared 30 mg versus 60 mg of iron, recorded no difference in the birth outcomes between these two groups, but neither did MMS compared with either of the two iron controls (2). Thus, combining nutrients in a supplement may result in nutrient-nutrient interactions, specifically between iron and zinc but also between other nutrients, which are all not well understood, especially since multiple possible combinations exist across the 14–15 micronutrients, resulting in numerous potential multiway interactions.

The other question that has been posed is whether a single RDA of these nutrients is sufficient to correct the existing micronutrient deficiencies, especially when pregnancy provides a narrow window of opportunity during which to intervene. Only two studies can speak to this issue for birth outcomes. The studies in Guinea-Bissau (51) and Tanzania (33) used two times or multiples of RDAs of nutrients and found significant effects on birth weight. The study in Guinea-Bissau (51) even showed that the same supplement formulation with a single RDA of nutrients did not increase birth weight. In Nepal, assessment of maternal status using numerous biochemical indicators revealed a significant reduction in deficiencies of numerous vitamins and minerals with a single RDA MMS (20). However, for many nutrients, deficiencies were not corrected fully. Although these data are intriguing, they are insufficient to serve as the basis for policy and program recommendations for a universal supplement containing multiples of RDAs for use in developing countries.

The other puzzling piece is that of the suggested increased risk of mortality due to MMS despite the increase in birth weight, which is expected to translate into beneficial gains in survival. Explanations have so far focused on an upward shift in the entire distribution of birth weight with the MMS and increase in larger babies (53), putting them at an increased risk of mortality (26). In Nepal, MMS was also found to increase the risk of birth asphyxia in the neonates (19). Other explanations include increased uterine sensitivity to oxytocin (22). In contrast to MMS, iron supplementation as examined in one study only increased birth weight in the left tail of the distribution and did not result in an increased risk of neonatal morbidity or mortality (19, 53).

The recent meta-analysis of the 12 trials showing significant increase in large-for-gestational-age babies due to MMS versus iron-folic acid (31) corroborates the early Nepal study findings of increased high birthweight babies (21). The meta-analysis also found a significant interaction between MMS and maternal BMI; MMS increased birth weight largely among women with a high BMI (31). This suggests that the action of micronutrients may require utilization of energy and protein as substrates. In fact, B-complex vitamins—specifically riboflavin, niacin, and thiamin—each play a major role in energy, fat, and protein metabolism. The major forms of niacin are the cellular pyridine nucleotides. NAD-dependent enzymes are involved in β-oxidation of fatty acyl coA, oxidation of ketone bodies and degradation of carbohydrate, and catabolism of amino acids. Riboflavin is essential for the synthesis of coenzymes that function in oxidation-reduction reactions involved in the catabolism of glucose, fatty acids, ketone bodies, and amino acids. Flavoenzymes participate in numerous pathways of energy production via the respiratory chain, whereas thiamin coenzyme (TPP) functions in prime interconversions of sugar phosphates and in decarboxylation reactions with energy production from α-keto acids. Thus, supplementation with these vitamins during pregnancy may perhaps have enhanced or increased efficiency of energy utilization and availability for fetal growth, especially among women with higher BMI.

On the other hand, vitamins B-12 and B-6 are more like folic acid in their biochemical activity as 1-C units in a variety of reactions; therefore, also like folic acid, they may not be associated with increases in birth weight. However, the biology of the differential effect

observed with multiple micronutrients needs further investigation. Recently, a study in rural Burkina Faso examined the impact of a MMS alone versus a food supplement fortified with multiple micronutrients (48). After adjusting for gestational age, the fortified food supplement had a significant impact on birth length compared with MMS alone, although the effect on birth weight was modest (31 g) and not significant.

It would be important also to re-examine the previously assumed strong linear inverse relationship between birth weight and infant mortality. Birth weight may be a proxy measure of infant health, and when used as a main outcome measure in trials, was only modestly enhanced with MMS, an increase that paradoxically conferred no survival advantage. It has been questioned whether absolute changes in birth weight are important for altering survival (78). For example, preterm birth or FGR may have a direct effect on mortality without birth weight being in the causal pathway. Between preterm birth and fetal growth restriction, the two main biologic factors leading to low birth weight, preterm has a stronger association with infant mortality than FGR (18). The MMS studies found no impact on preterm birth or duration of gestation. On the other hand, iron-folic acid in three trials was found to increase gestational age of pregnancy or reduce preterm (27, 100, 115). These relationships need further scrutiny, and studies testing nutritional interventions need to examine both components of birth weight as well as outcomes directly measuring fetal health, such as perinatal and neonatal mortality.

SUMMARY AND CONCLUSION

Maternal micronutrient deficiencies are widespread, and their prevention is important. However, most approaches to address these deficiencies have focused largely on the narrow period during pregnancy, primarily for the potential for these micronutrients to enhance birth outcomes. It is unlikely that supplementation or other approaches limited to the pregnancy period would eliminate micronutrient deficiencies that stem from chronic dietary inadequacies. Thus, it is crucial that any policy of antenatal multiple micronutrient strategy is grounded in scientific evidence of efficacy (benefit with respect to a range of health outcomes) and safety (posing minimal risk for all major outcomes). Current evidence suggests that multiple micronutrients may contribute only modestly to improvements in birth weight and have no impact on gestational length or fetal or neonatal survival. Thus, evidence to date does not indicate the widespread use of multiple micronutrients during pregnancy. Conversely, there seems to be strong evidence that the existing policy for antenatal iron-folic acid use is sound, as new evidence has revealed the beneficial impact of iron supplementation on outcomes beyond birth weight, such as neonatal and child survival. What is needed is urgent energizing of the failing antenatal care programs and delivery of iron-folic acid to pregnant women in many low- and middle-income countries.

Finally, data on the burden of maternal micronutrient deficiencies beyond iron, vitamin A, and zinc is limited. Thus, the prevalence and severity of concurrent maternal micronutrient deficiencies needs to be estimated using broadly representative populations in each high-risk region of the world. Furthermore, increasing evidence suggests that pre- and periconceptional maternal micronutrient nutriture can influence fetal and infant health (15); this merits further discussion for a critical research strategy.

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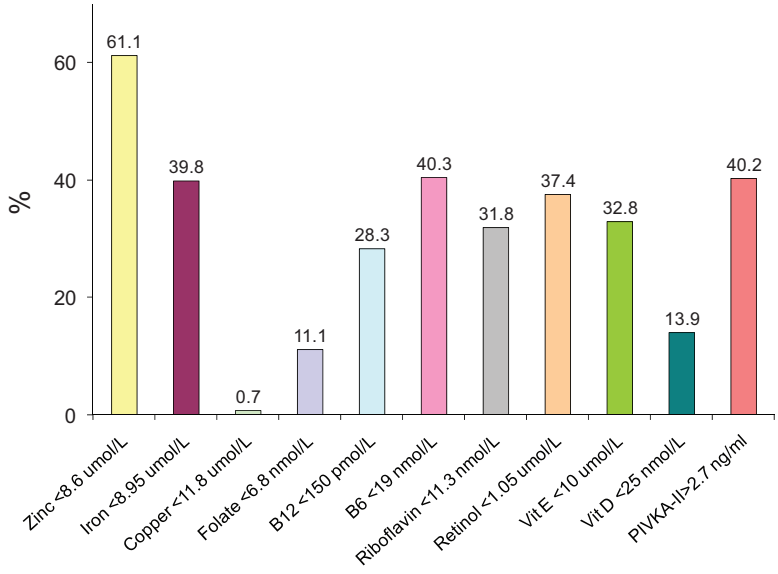

Figure 1

Prevalence of micronutrient deficiencies during the first trimester among pregnant women in Nepal (50).

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Errata

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